UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,448	03/08/2007	Pascal Drevet	033339/317269	9114

826 7590 03/15/2012

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
SNYDER, STUART	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
03/15/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,448	DREVET ET AL.	
	Examiner	Art Unit	
	STUART W. SNYDER	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *35-38,42-53,55-57 and 67-78* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *35-38,42, 46, 48-49,53, 55-57, 67-69,73, and 75-78* is/are rejected.

8)☒ Claim(s) *43-45,47,50-52,70-72 and 74* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply; PTO-1661*.

DETAILED ACTION

Election/Restrictions

1. Claims 35-38, 42-53, 55-57 and 67-78 are pending pursuant to Applicants' election with traverse of Group I in the reply filed on 11/7/2008.

Status of the Claims

2. Amendment of claims 35-37, 45 and 47; and cancellation of claims 40 and 41 in Applicants' filing of 12/29/2011 is acknowledged.

Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Claim 45 recites SEQ ID NO: 1. However, no computer readable form of the sequence listing has been received by the Office; neither has a statement that the CFR is the same as the previously submitted paper copy.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time

may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 35-53, 55-57 and 67-79 were previously rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, the claims were rejected for failing to convey that the inventors possessed an HIV immunogenic composition comprising embodiments of the claimed invention other than modified Tat-encoded polypeptides comprising mutations of all seven cysteine residues mutated to leucine, isoleucine, phenylalanine, tryptophan and tyrosine or derivitized by S-*tert*-butyl and triple cysteine mutations with derivatization by S-tert-butyl.

Rejection of the claims is **withdrawn** in view of amendment of claim 35.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 35-36, 44, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto, *et al.* (A novel RNA motif that binds efficiently and specifically to the Tat protein of HIV and inhibits the *trans*-activation by Tat of transcription *in vitro* and *in vivo*. Genes to Cells. 2000; 5: 371-388). The claims are drawn to an immunogenic composition comprising, *inter alia*, at least one isolated Tat antigen and a non-metal ligand of Tat. Additional limitations of the claims are the following: The non-metal ligand is, *inter alia*, a nucleotide (claim 36); the Tat antigen is, *inter alia*, a Tat protein or an immunogenic fragment thereof (claim 44); and the Tat protein or fragment thereof is a monomer (claim 48).

Yamamoto, *et al*. teaches Tat protein and an immunogenic peptide thereof derived from HIV-1 and HIV-2 that binds to an RNA aptamer (see page 384 at “Synthesis of Tat peptides and RNAs”; page 386 at “Assay of transcription *in vitro*"; page 386 at "Analysis of effects of RNA^{Tat} and TAR-1 RNA *in vivo* using a reporter system in HeLa cells"). For the first series of experiments, two Tat-derived peptides were synthesized from Tat amino acid positions 37-72 (CQ) and 66-97 (CP) from HIV-1 and HIV-2 sequences, respectively, the purified peptides and synthetic *trans*-activation response region (TAR) or RNA aptamers were incubated together to allow binding (see page 374 at “Binding kinetics” and Figure 2). For the second set of experiments, a luciferase gene under the control

of the HIV-1 promoter was incubated in the presence of HIV-1 Tat protein in an *in vitro* transcription system to determine inhibition of Tat-dependent transcription; Tat protein bound to either the HIV-1 TAR or the RNA inhibitors (see page 381 at "Effect of RNA^{Tat} on Tat-dependent transcription in a cell-free transcription assay" and Figure 8). Finally, an *in vivo* demonstration of Tat protein inhibition by the RNA inhibitors was performed in transduced HeLa cells; Tat protein bound to either TAR or the RNA inhibitors (see pages 381-382 at "Evaluation *in vivo* of TAR and RNA^{Tat} as decoys for sequestering Tat-1" and Figure 9).

Regarding the limitation of immunogenicity of Tat protein and peptide fragments thereof: It is well known in the virological arts that Tat protein is immunogenic. Furthermore, it is generally accepted that peptides longer than 10 amino acids are immunogenic at least when conjugated to a carrier such as Keyhole Limpet Hemocyanin. Thus, the limitation is implicit in the teachings of Yamamoto, *et al.* regarding the use of Tat proteins and peptide fragments thereof bound to non-metal ligands.

Thus, each and every limitation of claims 35-36, 44 and 48 is taught by Yamamoto, *et al.* and the claims are properly rejected under 35 U.S.C. 102(b).

6. Claims 35- 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Chang, *et al.* (HIV-1 Tat protein exits from cells via a leaderless secretory pathway and binds to extracellular matrix-associated heparin sulfate proteoglycans through its basic region. AIDS. 1997; 11:1421–1431). The

limitations of claim 35 is described above in section 4. Claims 37 and 38 add the limitations that the non-metal ligand of Tat protein is, *inter alia*, a heparin sulfate having a molecular weight of either 6000 or 15000 Da.

Chang, *et al.* teaches a method of determining Tat-heparin sulfate binding kinetics and a method of purification of HIV-1 Tat protein comprising heparin-Sepharose® affinity chromatography. HIV-1 Tat protein was extracted from Tat-transfected COS-1 cells and incubated with heparin sulfate to determine binding parameters (see page 1424 at "Gel shift assay" and page 1427 at "Soluble and HSPC-bound extracellular Tat" and Fig. 2). In separate experiments, Tat protein was purified using heparin-Sepharose® (see page 1424 at Purification of recombinant Tat protein by heparin affinity chromatography" and page 1428 at "Purification of a highly biologically active recombinant Tat protein by heparin-affinity chromatography" and Fig. 3). The heparin used in the methods is a mucopolysaccharide consisting of a repeating dimer of alpha-L-dipyranuronic acid 2-sulfate, and 2-deoxy-2-sulfamino-alpha-D-glucopyranose 6-sulfate, with a molecular weight range of 5 000-30 000.

Thus, each and every limitation of claims 35, 37 and 38 is taught by Chang, *et al.* and the claims are properly rejected under 35 U.S.C. 102(b).

7. Claims 35, 42, 55 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Silvera, *et al.* (Outcome of Simian-Human Immunodeficiency Virus Strain 89.6p Challenge following Vaccination of Rhesus Macaques with Human

Immunodeficiency Virus Tat Protein. J. Virol. 2002; 76(8): 3800–3809). The limitations of claim 35 is described above in section 4. Claims 42, 55 and 56 add the limitations of an inactivated, immunogenic Tat protein and a pharmaceutically acceptable composition thereof.

Silvera, *et al*. teaches immunization of Rhesus macaques with inactivated HIV-1 Tat protein. Chemically inactivated Tat protein was prepared with incomplete Freund's adjuvant and injected into macaques (see page 3801 at Materials and Methods, Immunization schedule). Sera from the macaques were analyzed for the presence of Tat protein-specific antibodies by ELISA (see page 3801 at Materials and Methods, Detection of anti-Tat and anti-SIV antibodies). Tat protein-specific antibodies were elicited by the immunization protocol as evidenced by detection of Tat protein-specific antibodies in immunized macaques' sera (see page 3802 at Results, Circulating anti-Tat antibodies and Table 3). Tat-specific T-cell responses were also elicited by Tat protein immunization of macaques (see page 3803 at Results, T-cell responses and epitope mapping; page 3804 at Fig. 2; page 3803 at Results, Tat-specific IFN-γ-producing $CD4^+$ and $CD8^+$ T cells; and page 3805 at Fig. 3). Finally, immunogenic epitopes were determined by B-cell epitope mapping (see page 3802 at Results, Mapping linear immunogenic B-cell epitopes).

Thus, each and every limitation of claims 35, 42, 55 and 56 is taught by Silvera, *et al*. and the claims are properly rejected under 35 U.S.C. 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Silvera, *et al.* in view of Zagury, *et al.* (WO 01/43771 A1). The claim is drawn to an inactivated immunogenic composition of Tat protein comprising alumina hydroxide. The teachings of Silvera, *et al.* and relevance to claim 56, on which the instantly rejected claims depend, is described above in section 6; Silvera, *et al.* does not teach alumina hydroxide as adjuvant in Tat protein immunogenic compositions.

Zagury, et al. teaches immunogenic Tat protein compositions comprising alumina hydroxide in at least the claims. The following is a machine translation of claims 4, 5, and 10:

> 4. Use according one of claims 1, 2 and 3 characterized in that it is composed of immunogenic proteins derived from an immunosuppressive and/or angiogenic [selected from the] following:
>
> Tat protein of HIV-1,
>
> Tax protein of an HTLV-1,
>
> E7 protein of the papilloma virus, [and]

mannan-dependent lectin produced by activated immune cells.

5. Use according one of claims 1 2 and 3, characterized in that it consists [of an] immunogen treated with an aldehyde, or carboxamide, or carboxymethyl or maleimide.

10. A pharmaceutical vaccine composition according to claim 8 or 9 characterized in that it contains an adjuvant adsorbent active ingredient, such alumina hydroxide or gold particles.

Zagury, et al. clearly teaches immunogenic Tat protein compositions, inactivated immunogenic compositions and vaccine compositions comprising alumina hydroxide.

A skilled artisan would have found it obvious to use alumina in an immunogenic, inactivated Tat protein composition. The skilled artisan would have been motivated to increase the immune response to the protein. The skilled artisan would have a reasonable expectation of success because alumina hydroxide is one of the few adjuvants that have been proven safe and effective for use as an adjuvant according the US FDA. Thus, the invention of claim 57 is *prima facie* obvious over the combination of Silvera, *et al.* and Zagury, *et al.*; and the claims are properly rejected under 35 U.S.C. 103(a).

9. Claims 46, 49, 67-69, 73, and 75-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto, *et al.* in view of Frankel, *et al.* (Tat Protein from Human Immunodeficiency Virus Forms a Metal-Linked Dimer. Science.

1998; 240(4848): 70-73). The claims are drawn to an immunogenic composition of Tat protein that are oligomer and/or comprise metal ions. The teachings of Yamamoto, *et al*. and relevance to claim 35, on which the instantly rejected claims ultimately depend, is described above in section 3; Yamamoto, *et al*. does not teach oligomeric and/or metal ion-containing Tat protein immunogenic compositions.

Frankel, *et al*. teaches Tat protein compositions comprising Zn^{++}- or Cd^{++}-containing dimers of the protein. The protein complexes were analyzed by UV spectroscopy to demonstrate metal binding (see page 70 at the last paragraph and page 71 at Fig. 1(A)). And by circular dichroism to demonstrate dimerization (see page 71 at Fig. 1(B) and page 72 at column 3 and Fig. 4). Thus, the combination of Yamamoto, *et al*. and Frankel, *et al*. teaches each and every limitation of claims 46, 49, 67-69, 73, and 75-78.

A skilled artisan would have found it obvious to form dimers of Tat proteins using divalent metal ions. The skilled artisan would have been motivated to prepare Tat protein immunogens that mimic putative *in vivo* Tat protein complexes, as taught by Frankel, *et al*. (see page 73 at last paragraph). The skilled artisan would have a reasonable expectation of success because the dimeric Tat protein, divalent metal complexes are recognized by Tat protein specific antibodies as taught by Frankel, *et al*. (see page 71 at Fig. 2). Thus, the invention of claims 46, 49, 67-69, 73, and 75-78 is *prima facie* obvious over the combination of Yamamoto, *et*

al. and Frankel, *et al.*; and the claims are properly rejected under 35 U.S.C. 103(a).

Allowable Subject Matter

10. Claims 43, 45, 47, 50-52, 70-72, and 74 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STUART W. SNYDER whose telephone number is (571)272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ZACHARIAH LUCAS can be reached on (571)272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648

/STUART W SNYDER/
Examiner, Art Unit 1648

sws